PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

PRIVETT, Kathryn, Louise
SmithKline Beecham
Corporate Intellectual Property
(CN9.25.1)
980 Great West Road
Brentford
Middlesex TW8 9GS
ROYAUME-UNI

**Date of mailing** (day/month/year)
19 February 2002 (19.02.02)

**Applicant's or agent's file reference**
FB/b45194

**IMPORTANT NOTIFICATION**

**International application No.**
PCT/EP00/07965

**International filing date** (day/month/year)
15 August 2000 (15.08.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
PRIVETT, Kathryn, Louise
Corporate Intellectual Property
SmithKline Beecham
Two New Horizons Court
Brentford
Middlesex TW8 9EP
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: +44 20 8975 2585
Facsimile No.: +44 20 8975 6294
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
PRIVETT, Kathryn, Louise
SmithKline Beecham
Corporate Intellectual Property
(CN9.25.1)
980 Great West Road
Brentford
Middlesex TW8 9GS
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: +44 20 8047 5000
Facsimile No.: +44 20 8047 6894
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**
Facsimile No.: (41-22) 740.14.35

Authorized officer
Anman QIU
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>12 June 2001 (12.06.01) | |
| **International application No.**<br>PCT/EP00/07965 | **Applicant's or agent's file reference**<br>FB/b45194 |
| **International filing date** (day/month/year)<br>15 August 2000 (15.08.00) | **Priority date** (day/month/year)<br>17 August 1999 (17.08.99) |
| **Applicant**<br>COLAU, Brigitte, Desiree, Alberte et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 March 2001 (14.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12797 A3

(51) International Patent Classification[7]: A61K 39/15, C12N 7/08

(21) International Application Number: PCT/EP00/07965

(22) International Filing Date: 15 August 2000 (15.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9919468.0 17 August 1999 (17.08.1999) GB
9927336.9 18 November 1999 (18.11.1999) GB

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM BIOLOGICALS S.A.** [BE/BE]; Rue de l'Institut 89, B-1330 Rixensart (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COLAU, Brigitte, Desiree, Alberte** [BE/BE]; Smithkline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart ø (BE). **DENAMUR, Françoise** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **KNOTT, Isabelle** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **POLISZCZAK, Annick** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **THIRY, Georges** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). **VANDE VELDE, Vincent** [BE/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE).

(74) Agent: **PRIVETT, Kathryn, Louise**; Corporate Intellectual Property, SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

(88) Date of publication of the international search report:
2 August 2001

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 01/12797 A3

(54) Title: METHOD OF SEPARATING ROTAVIRUS VARIANTS AND LIVE ATTENUATED ROTAVIRUS VACCINE

(57) Abstract: The invention provides an attenuated rotavirus population comprising a single variant or substantially a single variant which is defined by a nucleotide sequence encoding at least one of the major viral proteins designated as VP4 and VP7. The invention particularly provides a rotavirus population designated as P43. The invention further provides a novel formulation for a rotavirus vaccine which is in the form of a quick dissolving tablet for immediate dissolution when placed on the tongue.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07965

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/15 C12N7/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, PAJ, WPI Data, MEDLINE, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 4 571 385 A (GREENBERG HARRY B ET AL)<br>18 February 1986 (1986-02-18)<br>column 5, line 66 -column 6, line 13<br>--- | 14,15 |
| X | MIDTHUN K ET AL: "Single gene substitution rotavirus reassortants containing the major neutralization protein (VP7) of human rotavirus serotype 4"<br>JOURNAL OF CLINICAL MICROBIOLOGY,<br>vol. 24, no. 5, October 1986 (1986-10),<br>pages 822-826, XP000881407<br>ISSN: 0095-1137<br>the whole document<br>--- | 1-32,39 |
| A | US 4 341 763 A (ZYGRAICH NATHAN)<br>27 July 1982 (1982-07-27)<br>the whole document<br>--- | 1-32,39 |
| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 25 January 2001 | 12/02/2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax (+31–70) 340–3016 | Nichogiannopoulou, A |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | GARBAG-CHENON A ET AL: "Reactogenicity and immunogenicity of rotavirus WC3 vaccine in 5-12-month old infants" RESEARCH IN VIROLOGY, vol. 140, no. 3, 1989, pages 207-217, XP000973268 ISSN: 0923-2516 abstract | 1-32,39 |
| A | BERNSTEIN DAVID I ET AL: "Safety and immunogenicity of live, attenuated human rotavirus vaccine 89-12." VACCINE, vol. 16, no. 4, February 1998 (1998-02), pages 381-387, XP004099298 ISSN: 0264-410X cited in the application the whole document | 1-32,39 |
| A | MIDTHUN K ET AL: "ROTAVIRUS VACCINES: AN OVERVIEW" CLINICAL MICROBIOLOGY REVIEWS,US,WASHINGTON, DC, vol. 9, no. 3, July 1996 (1996-07), pages 423-434, XP000872603 ISSN: 0893-8512 the whole document | 1-32,39 |
| A | DATABASE EMBL 'Online! ROHVP4OCP, 4 July 1994 (1994-07-04) PADILLA-NORIEGA L ET AL: "Human rotavirus outer capsid protein (VP4) gene" XP002158486 VP4 sequence with 98.7% identity over 2350 nt of SEQ ID No: 1 abstract | 10 |
| A | DATABASE EMBL 'Online! HRU88717, 9 March 1997 (1997-03-09) CRAWFORD SE ET AL: "Human rotavirus glycoprotein VP7 mRNA" XP002158487 VP7 sequence with 98.7% identity over 1014 nt of SEQ ID No: 2 abstract | 10 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/07965

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4571385 A | 18-02-1986 | AT 65698 T | 15-08-1991 |
| | | AU 584582 B | 01-06-1989 |
| | | AU 3150584 A | 25-01-1985 |
| | | CA 1217422 A | 03-02-1987 |
| | | DE 3484863 A | 05-09-1991 |
| | | EP 0130906 A | 09-01-1985 |
| | | JP 2084776 C | 23-08-1996 |
| | | JP 6197761 A | 19-07-1994 |
| | | JP 7112432 B | 06-12-1995 |
| | | JP 7057191 B | 21-06-1995 |
| | | JP 60501639 T | 03-10-1985 |
| | | LU 90472 A | 16-03-2000 |
| | | WO 8500184 A | 17-01-1985 |
| US 4341763 A | 27-07-1982 | NONE | |

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
|---|---|---|
| FB/B45194 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/EP 00/ 07965 | 15/08/2000 | 17/08/1999 |
| Applicant | | |
| SMITHKLINE BEECHAM BIOLOGICALS S.A. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHOD OF SEPARATING ROTAVIRUS VARIANTS AND LIVE ATTENUATED ROTAVIRUS VACCINE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

12

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| FB/B45194 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP00/07965 | 15/08/2000 | 17/08/1999 |
| International Patent Classification (IPC) or national classification and IPC | | |
| C12N15/00 | | |
| Applicant | | |
| SMITHKLINE BEECHAM BIOLOGICALS S.A. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 14/03/2001 | 22.01.2002 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Nichogiannopoulou, A<br>Telephone No. +49 89 2399 8054 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/07965

## I. Basis of the r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-41 as originally filed

**Claims, No.:**

1-39 as received on 04/01/2002 with letter of 03/01/2002

**Drawings, sheets:**

1/6-6/6 as originally filed

**Sequence listing part of the description, pages:**

1-7, filed with the letter of 5.12.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 39.

because:

☒ the said international application, or the said claims Nos. 39 relate to the following subject matter which does not require an international preliminary examination (*specify*):
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-39 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-39 |
| Industrial applicability (IA) | Yes: | Claims | 1-38 |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

**Re Item I**

**Basis of the opinion**

1. The amendments filed with the letter of 03.01.2002 are formally allowable under Article 34(2)(b) PCT because they do not introduce subject-matter extending beyond the content of the application as filed.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. Claim 39 -since it concerns *in vivo* methods- relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

   D1: US-A-4 571 385 (GREENBERG H ET AL) 18 February 1986 (1986-02-18)

   D2: MIDTHUN K ET AL: 'Single gene substitution rotavirus reassortants containing the major neutralization protein (VP7) of human rotavirus serotype 4' JOURNAL OF CLINICAL MICROBIOLOGY, vol. 24, no. 5, October 1986 (1986-10), pages 822- 826, XP000881407 ISSN: 0095-1137

   D3: US-A-4 341 763 (ZYGRAICH NATHAN) 27 July 1982 (1982-07-27)

   D4: GARBAG-CHENON A ET AL: 'Reactogenicity and immunogenicity of rotavirus

WC3 vaccine in 5-12-month old infants' RESEARCH IN VIROLOGY, vol. 140, no. 3, 1989, pages 207-217, XP000973268 ISSN: 0923-2516

2. **Novelty** (Article 33(2) PCT)

The present application discloses that the previously used live attenuated oral human rotavirus vaccine (P26 from strain 89-12) comprises a mixture of variants (at least three VP4 gene variants) and is therefore not a reliably consistent population for the production of vaccine lots. A method for separating human rotavirus variants and an improved live attenuated human rotavirus vaccine derived from a cloned human rotavirus strain is disclosed. A vaccine composition comprising live attenuated human rotavirus in lyophilised form is also claimed.

The available prior art (**D1-D4**) disclose subject-matter related to either human/animal reassortant rotaviruses (**D1** and **D2**) or animal rotaviruses (**D3** and **D4**). The present application is restricted to human rotaviruses and is thus novel over the available prior art under the terms of Article 33(2) PCT.

3. **Inventive step** (Article 33(3) PCT)

3.1. **D2** is a publication disclosing the selection of attenuated reassortant (animal/human recombinants) rotaviruses comprising the human VP7 antigen. Single reassortants were cloned by individual plaque isolation encoding a single VP7 antigen. The genotype of the cloned reassortants was verified by RNA-RNA hybridisation. The present application differs from **D2** in the use of human rotaviruses. It is however considered that this choice would have been obvious to the skilled person given the great interest in effective rotavirus vaccines and the disappointing results obtained sofar (see description pages 1, 2). **D2** is thus found to be detrimental to the inventive step of new claims 1-32 and 39.

3.2. **D4** is a publication disclosing a bovine rotavirus (WC3) vaccine in lyophilised form. The virus was attenuated by serial passages in cell culture. New claims 33-38 differ from **D4** in the use of human rotaviruses. It is however considered that this choice

would have been obvious to the skilled person given the great interest in effective rotavirus vaccines and the disappointing results obtained sofar (see description pages 1, 2). **D4** is thus detrimental to the novelty and inventive step of claims 33-38.

3.3. For the sake of completion it is noted that **D3** also discloses live attenuated bovine rotavirus vaccine in lyophilised form, thus being detrimental to the inventive step of claims 33-38.

4. **Industrial applicability** (Article 33(4) PCT)
The subject-matter of claims for which an opinion has been established (see item III) is considered industrially applicable, fulfilling the requirements of Article 33(4) PCT.

PATENT
ATTORNEY'S DOCKET NUMBER B45194

# TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE (DO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371

| INTERNATIONAL APP. NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/EP00/07965 | 15 August 2000 | 17 August 1999 |

TITLE OF INVENTION
VACCINE

APPLICANT(S) FOR DO/US
Brigitte Desiree Alberte COLAU, Francoise DENAMUR, Isabelle KNOTT, Annick POLISZCZAK, Georges THIRY, Vincent VANDE VELDE

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231
ATTENTION: DO/US

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Transmittal Letter, Form PTO 1390 and the papers indicated as being transmitted therewith, and Post Card are being deposited with the United States Postal Service on this date February 6, 2002 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EV000522293US addressed to the:
Assistant Commissioner for Patents, Washington, D.C. 20231.

Elsa Matos
(Typed or printed name of person mailing paper)

Elsa Matos
(Signature of person mailing paper)

## CLAIMS

1. An attenuated rotavirus population, characterised in that it comprises a single variant or substantially a single variant, said variant defined by a nucleotide sequence encoding at least one of the major viral proteins designated as VP4 and VP7.

2. A rotavirus population according to claim 1 which is a cloned strain.

3. A rotavirus population according to claim 1 or claim 2 which is derived from a human rotavirus infection.

4. A rotavirus population according to any one of claims 1 to 3 which replicates in and is excreted by humans.

5. A rotavirus population according to any one of claims 1 to 4 in which the substantially single variant is a variant in which the VP4 gene comprises a nucleotide sequence comprising at least one of the following: an adenine base (A) at position 788, an adenine base (A) at position 802 and a thymine base (T) at position 501 from the start codon.

6. A rotavirus population according to claim 5 in which the VP4 gene comprises a nucleotide sequence comprising an adenine base (A) at positions 788 and 802 and a thymine base (T) at position 501 from the start codon.

7. A rotavirus population according to any one of claims 1 to 6 in which the substantially single variant is a variant in which the VP7 gene comprises a nucleotide sequence comprising at least one of the following: a thymine (T) at position 605, an adenine (A) at position 897 and a guanine (G) at position 897 from the start codon.

8. A rotavirus population according to claim 7 in which the VP7 gene comprises a nucleotide sequence comprising a thymine (T) at position 605 and an adenine (A) or a guanine (G) at position 897 from the start codon.

9. A rotavirus population according to claims 5 to 8, in which the VP4 gene comprises a nucleotide sequence comprising an adenine (A) at positions 788 and 802 and a thymine (T) at position 501 from the start codon; and the VP7 gene comprises a nucleotide sequence comprising a thymine (T) at position 605 and an adenine (A) at position 897 from the start codon.

10. A rotavirus which comprises a nucleotide sequence encoding a VP4 protein wherein the nucleotide sequence is as shown in Figure 1, and/or a nucleotide sequence encoding a VP7 protein wherein the nucleotide sequence is as shown in Figure 2.

11. A rotavirus population according to any one of claims 1 to 10, designated as P43 and deposited under accession number ECACC 99081301.

12. A rotavirus variant designated P43 and deposited with the ECACC under accession number 99081301, rotavirus progeny and immunologically active derivatives thereof and materials obtained therefrom.

13. A rotavirus reassortant comprising at least one antigen or at least one segment of the rotavirus variant P43 according to claim 11 or claim 12.

14. A method of producing a purified rotavirus population comprising a substantially single variant, the method comprising:

passaging a rotavirus preparation on a suitable cell line;

optionally selecting homogeneous culture using the steps of either:

limit dilution; or

individual plaque isolation; and

checking for the presence of a substantially single variant by sequencing an appropriate region of the VP4 and/or VP7 gene sequence.

15. A method according to claim 14 in which the rotavirus preparation is passaged on AGMK cells.

16. A method according to claim 14 or claim 15 in which the rotavirus preparation has the characteristics of an 89-12 strain or derivative thereof.

17. A method according to any one of claims 14 to 16, which comprises the additional step of ether treatment to remove adventitious ether-sensitive contaminating agents.

18. A vaccine composition comprising a live attenuated virus according to any one of claims 1 to 13 admixed with a suitable pharmaceutical carrier or adjuvant.

19. A vaccine composition according to claim 18 adapted for oral administration.

20. A vaccine composition according to claim 19 in which the live attenuated virus is formulated with an antacid composition.

21. A vaccine composition according to claim 20, wherein the antacid composition comprises an organic antacid.

22. A vaccine composition according to claim 21, wherein the antacid is sodium citrate.

23. A vaccine composition according to claim 20, wherein the antacid composition comprises an inorganic antacid.

24. A vaccine composition according to claim 23, wherein the antacid is aluminium hydroxide.

25. A vaccine composition according to Claim 23, wherein the antacid is calcium carbonate.

26. A vaccine composition according to Claim 25, which further comprises a viscous agent.

27. A vaccine composition accorsing to Claim 26, wherein the viscous agent is xanthane gum.

28. A vaccine composition according to any one of claims 25 – 27 wherein the live attenuated virus is formulated with calcium carbonate and xanthane gum and reconstituted with aqueous solution.

29. A vaccine composition according to any one of claim 20 to 28, wherein the live attenuated virus is formulated with the antacid composition and lyophilised in a blister pack.

30. A vaccine composition according to any one of claims 18 to 29, wherein the virus is in lyophilised form.

31. A vaccine composition according to claim 30, wherein the live attenuated virus and the antacid composition are present in separate containers for formulation as a liquid vaccine composition prior to administration.

32. A vaccine composition according to claim 30, wherein the live attenuated virus and the antacid composition are present in the same container for formulation as a lyophilised vaccine composition to be recontituted with aqueous solution prior to administration.

33. A vaccine composition comprising a live attenuated rotavirus virus wherein the virus is in lyophilised form.

34. A vaccine composition according to Claim 33 wherein the composition is in the form of a quick dissolving tablet for immediate dissolution when placed on the tongue.

35. A vaccine composition according to claim 33 or claim 34 comprising a lyophilised live attenuated rotavirus admixed with an inorganic antacid such as calcium carbonate and a viscous agent such as xanthane gum.

36. A vaccine composition according to claim 35, wherein the attenuated virus and the antacid composition are present in separate containers for formulation as a liquid vaccine composition prior to administration.

37. A vaccine composition according to claim 35, wherein the attenuated virus and the antacid composition are formulated in the same container, as a lyophilised vaccine composition to be reconstituted with aqueous solution prior to administration.

38. A method of manufacture of a rotavirus vaccine comprising admixing a lyophilised live attenuated human rotavirus with an antacid and a viscous agent.

39. A method of preventing rotavirus infection in humans by administering to a human subject in need thereof an effective amount of a vaccine according to any one of claims 18 to 27.